

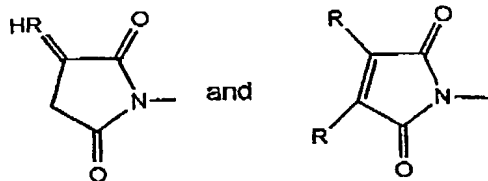
CLAIMS

1. An aqueous composition comprising an amphiphilic block copolymer having a hydrophilic block and a hydrophobic block, dispersed in the solution, and a biologically active compound associated with the polymer, characterised in that the hydrophilic block has pendant zwitterionic groups.
2. A composition according to claim 1 in which the biologically active molecule is associated by hydrophobic interactions with the copolymer.
3. A composition according to claim 2 in which the biologically active compound has a measured and/or calculated partition coefficient between octanol and water, log P or clog P of at least 1.0, preferably at least 1.5.
4. A composition according to any preceding claim in which the copolymer is dispersed in the form of micelles.
5. A composition according to any preceding claim wherein the hydrophilic block is formed by radical polymerisation of ethylenically unsaturated monomers.
6. A composition according to claim 5 in which the monomers comprise a zwitterionic monomer.
7. A composition according to claim 6 in which the zwitterionic monomer has the general formula

Y B X

I

in which Y is an ethylenically unsaturated group selected from $H_2C=CR-CO-A-$, $H_2C=CR-C_6H_4-A^1-$, $H_2C=CR-CH_2A^2$, $R^2O-CO-CR=CR-CO-O$, $RCH=CH-CO-O-$, $RCH=C(COOR^2)CH_2-CO-O$,

A is -O- or NR^1 ;A¹ is selected from a bond, $(CH_2)_lA^2$ and $(CH_2)_lSO_3^-$ in which l is 1 to

12;

A² is selected from a bond, -O-, O-CO-, CO-O, CO-NR¹-, -NR¹-CO, O-CO-NR¹-, NR¹-CO-O-;

R is hydrogen or C₁₋₄ alkyl;

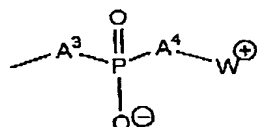
5 R¹ is hydrogen, C₁₋₄ alkyl or BX,

R² is hydrogen or C₁₋₄ alkyl;

B is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxaalkylene) group, optionally containing one or more fluorine substituents;

10 X is a zwitterionic group.

8. A composition according to claim 7 in which X is a group of the general formula II



II

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in which the moieties A³ and A⁴, which are the same or different, are -O-, -S-, -NH- or a valence bond, preferably -O-, and W⁺ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is preferably a C₁₋₁₂-alkanediyl group, preferably in which W⁺ is a group of formula

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-W¹-N⁺R³₃, -W¹-P⁺R⁴₃, -W¹-S⁺R⁴₂ or -W¹-Het⁺ in which:

25 W¹ is alkanediyl of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, or alkylene aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene or alkylene cycloalkyl alkylene, which group W¹ optionally contains one or more fluorine substituents and/or one or more functional groups; and

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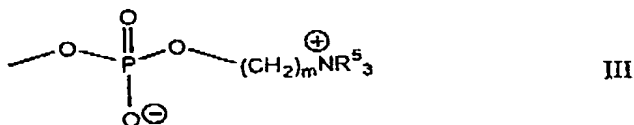
either the groups R³ are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl, or two

of the groups R^3 together with the nitrogen atom to which they are attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or the three groups R^3 together with the nitrogen atom to which they are attached as heteroaromatic ring having 5 to 7 atoms, either of which rings may be fused with another saturated or unsaturated ring to form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups R^3 is substituted by a hydrophilic functional group, and

the groups R^4 are the same or different and each is R^3 or a group OR^3 , where R^3 is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine.

9. A composition according to claim 7 in which X has the general formula III



where the groups R^5 are the same or different and each is hydrogen or C_{1-4} alkyl, and m is from 1 to 4, in which preferably the groups R^5 are the same preferably methyl.

10. A composition according to any of claims 7 to 9 in which Y is $H_2C=CR-CO-A-$ in which R is H or methyl and -A- is -O- or -NH-.

11. A composition according to any of claims 7 to 10 in which B is a C_{2-6} -alkanediyl group.

12. A composition according to any of claims 7 to 11 in which the zwitterionic monomer is 2-methacryloyloxyethyl-2'-trimethylammonium ethyl phosphate inner salt.

13. A composition according to any preceding claim in which the hydrophobic block comprises pendant groups which are ionisable, having a pK_A or pK_B in the range 4 to 10, preferably in the range 5 to 9, for instance in the range 6 to 8.

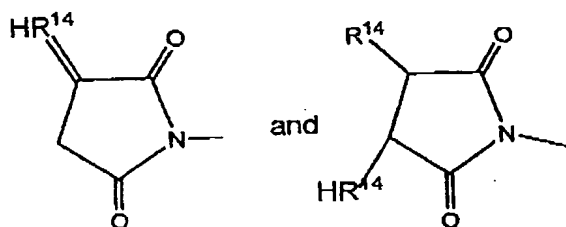
14. A composition according to claim 13 in which the hydrophobic block is formed by radical polymerisation of ethylenically unsaturated monomers.

15. A composition according to claim 14 in which the monomers from which the hydrophobic block is formed have the general formula VII



in which Y^1 is an ethylenically unsaturated group selected from $H_2C=CR^{40}-CO-A^8-$, $H_2C=CR^{14}-C_6H_4-A^8-$, $H_2C=CR^{14}-CH_2A^{10}$, $R^{16}O-CO-CR^{14}=CR^{14}-CO-O$, $R^{14}CH=CH-CO-O$, $R^{14}CH=C(COOR^{16})CH_2-CO-O$,

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A^8 is $-O-$ or NR^{15} ;

A^9 is selected from a bond, $(CH_2)_qA^{10}$ and $(CH_2)_qSO_3-$ in which q is 1 to

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12;

A^{10} is selected from a bond, $-O-$, $O-CO-$, $CO-O-$, $CO-NR^{41}-$, $-NR^{41}-CO$, $O-CO-NR^{15}-$, $NR^{15}-CO-O-$;

R^{14} is hydrogen or C_{1-4} alkyl;

R^{15} is hydrogen, C_{1-4} alkyl or B^1Q ;

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R^{16} is hydrogen or C_{1-4} alkyl;

B^1 is a bond, or a straight branched alkanediyl, alkylene oxaalkylene, or alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents; and

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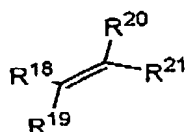
Q is a cationic or cationisable group of the formula $-NR^{17}_p$, $-PR^{17}_p$ and SR^{17}_r , in which p is 2 or 3, r is 1 or 2, the groups R^{17} are the same or different and each is selected from the group consisting of hydrogen, C_{1-24} alkyl and

aryl, or two of the groups R^{17} together with the heteroatom to which they are attached from a 5 to 7 membered heterocyclic ring or three R^{17} groups together with the heteroatom to which they are attached form a 5 to 7 membered heteroaromatic ring, either of which rings may be fused to another 5 to 7 membered saturated or unsaturated ring, and any of the R^{17} groups may be substituted by amino or hydroxyl groups or halogen.

16. A composition according to claim 15 in which Q is NR^{17}_2 in which each R^{17} is H or C_{1-4} -alkyl.

17. A composition according to claim 5 or claim 14 in which the ethylenically unsaturated monomers include comonomer.

18. A composition according to claim 17 in which the or each comonomer has the general formula VIII



VIII

in which R^{18} is selected from hydrogen, halogen, C_{1-4} alkyl and groups $COOR^{22}$ in which R^{22} is hydrogen and C_{1-4} alkyl;

R^{19} is selected from hydrogen, halogen and C_{1-4} alkyl;

R^{20} is selected from hydrogen, halogen, C_{1-4} alkyl and groups $COOR^{22}$ provided that R^{18} and R^{20} are not both $COOR^{22}$; and

R^{21} is a C_{1-10} alkyl, a C_{1-20} alkoxy carbonyl, a mono- or di- (C_{1-20} alkyl) amino carbonyl, a C_{6-20} aryl (including alkaryl) a C_{7-20} aralkyl, a C_{6-20} aryloxy carbonyl, a C_{1-20} -aralkyloxy carbonyl, a C_{6-20} arylamino carbonyl, a C_{7-20} aralkyl-amino, a hydroxyl or a C_{2-10} acyloxy group, any of which may have one or more substituents selected from halogen atoms, alkoxy, oligo-alkoxy, aryloxy, acyloxy, acylamino, amine (including mono and di-alkyl amino and trialkylammonium in which the alkyl groups may be substituted), carboxyl, sulphonyl, phosphoryl, phosphino, (including mono- and di- alkyl phosphine

and tri-alkylphosphonium), zwitterionic, hydroxyl groups, vinyloxy carbonyl and other vinylic or allylic substituents, and reactive silyl or silyloxy groups, such as trialkoxysilyl groups;

or R^{21} and R^{20} or R^{21} and R^{19} may together form $-\text{CONR}^{23}\text{CO}$ in which

5 R^{23} is a C_{1-20} alkyl group.

19. A composition according to claim 18 in which the comonomer is a C_{1-24} alkyl(alk)-acrylate or -acrylamide, mono- or di- hydroxy- C_{1-6} -alkyl(alk)-acrylate, or acrylamide, oligo(C_{2-3} alkoxy) C_{2-18} -alkyl (alk)-acrylate, or -acrylamide, styrene, vinylacetate or N-vinyl lactam.

10 20. A composition according to any preceding claim in which the polydispersity of molecular weight of each of the blocks is less than 2.0, preferably less than 1.5, more preferably in the range 1.1 to 1.4.

21. A composition according to any of claims 5 to 13 in which the degree of polymerisation of the hydrophilic block is in the range 2 to 1000, preferably 5 to 250, more preferably 10 to 100.

15 22. A composition according to any of claims 14 to 16 in which the degree of polymerisation of the hydrophobic block is in the range 5 to 2000, preferably 10 to 500, more preferably 20 to 250.

20 23. A composition according to claim 21 or 22 in which the ratio of the degrees of polymerisation of the hydrophobic to hydrophilic blocks is in the range 1:5 to 10:1, preferably 1:1 to 5:1.

24. A composition according to claim 5 in which the radical polymerisation is a controlled radical polymerisation.

25 25. A composition according to claim 24 in which the polymerisation is an atom transfer radical polymerisation or group transfer polymerisation.

26. A composition according to claim 25 in which the initiator for the radical transfer polymerisation process is a polymer compound in which the polymeric moiety is hydrophobic which forms the hydrophobic block of the copolymer.

30 27. A composition according to claim 25 in which the hydrophobic block is also formed from ethylenically unsaturated monomers by a radical

transfer polymerisation process.

28. A composition according to any preceding claim in which the biologically active molecule is a cytotoxic compound, preferably an anti-cancer drug.

5 29. A method of forming an aqueous composition comprising an amphiphilic block copolymer and a biologically active compound, in which the copolymer comprises a hydrophilic block and a hydrophobic block an aqueous dispersion of empty copolymer micelles is formed and the micellar dispersion is contacted with biologically active compound under conditions such that the
10 biologically active compound becomes associated with the copolymer in the micelles, characterised in that the hydrophilic block has pendant zwitterionic groups.

30. A method according to claim 29 in which the biologically active compound has a partition coefficient between octanol and water ($\log P$) of at
15 least 1.0, preferably at least 1.5, for instance 2.0 or higher.

31. A method according to claim 29 or claim 30 in which the hydrophobic block of the copolymer comprises ionisable groups, and in which the empty copolymer micelles are formed by a process comprising:

a) a first copolymer dissolution step in which the block copolymer,
20 with the groups of hydrophobic block in at least partially ionised form, is dissolved in an aqueous liquid, and

b) a second micelle forming step in which the conditions in the solution are adjusted so that the ionised groups are converted at least partially to their ionisable form, whereby the copolymer is above the critical micelle
25 concentration in the aqueous liquid and micelles are formed.

32. A method according to claim 31 in which the conditions which are adjusted are of temperature and/or pH.

33. A method according to claim 31 or 32 in which the ionisable groups are primary, secondary or tertiary amine groups and in which the
30 micelle forming step involves raising the pH whereby the ionised groups become deprotonated.

34. A method according to any of claims 29 to 33 in which the biologically active compound is in solid form when it is contacted with the aqueous dispersion of empty micelles.

5 35. A method according to any of claims 29 to 34 in which the biologically active compound is in solution in an organic solvent when it is contacted with the aqueous dispersion of empty micelles.

36. A method according to claim 29 having the further features of any of claims 2 to 28.